REMARKS/ARGUMENTS

Claims 2-27 are active.

Claims 18-25 are withdrawn based on the imposed restriction. Nonetheless, these non-elected claims are retained and depend from the elected subject matter of Claim 2 so that the Office may consider rejoinder upon determining that the elected product claims are allowable. With respect to the species election, Applicants reiterate their request to expand to the non-elected species upon finding that the elected specie is allowable.

Claim 2 is amended in accordance with the disclosure for the variable R^6 found on page 19, line 19 to page 22, line 15 of the specification and further to define that the C1-6alkyl C3-8cycloalkyl is unsubsituted . The remaining claims have been amended consistent with the amendments to Claim 2, from which these claims depend.

No new matter is added.

The rejection under 35 USC 112, first paragraph is addressed by the amendment to Claims 6 and 9 which aligns the definition of R^6 with Claim 2. Withdrawal of the rejection is requested.

The rejection in view of compounds 154 and 155 of JP 2002/53566 to Inaba and the rejections based on compounds identified from the CAS database are no longer applicable.

Inaba's compounds 154 and 155 at the corresponding R^6 position includes an acyl group C(O)R where R is a C_3-C_8-cycloalkyl. As acyl is not a substituent in Claim 2, these compounds are not within the scope of the claims. Also C1-6 alkyl C3-8 cycloalkyl substituted by oxy as interpreted by the Examiner is not within the substituents listed in the claims. Regarding Inaba, the Examiner views that the C_1-C_6 alkyl C_3-C_8 cycloalkyl can be substituted with, e.g., an oxo group, absent a specific limitation that requires that the C_1-

C_6alkyl C_3-C_8 cycloalkyl is unsubstituted. Although it was believed to be apparent from the previous submission, the C_1-C_6alkyl C_3-C_8 cycloalkyl has been defined as being in unsubstituted form.

With respect to the Examiner's statement regarding Claim 27 and the perceived overlap, Claim 27 has been amended to remove the species corresponding to citations b), o) (see the 10th and 12th species on page 22 of the claim listing) and citations i), q), n) and d) (see the 10th, 13th, 14th and 17th species on page 29 of the claim listing).

Regarding the obviousness rejection, the Examiner relies on Inaba but as discussed above Inaba, based on the limitation of Claim 2 that the C_1-C_6alkyl C_3-C_8 cycloalkyl is unsubstituted differs from Inaba.

Regarding the obviousness rejections citing Wu and Takaya, the Examiner characterizes each as generically describing the claimed compounds (see page 12 of the Action). The Examiner's rationale for modifying the Wu and Takaya references is found on page 13 of the Action: "[t]he motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., protein kinase Cγ inhibitors)."

Applicants acknowledge the Examiner's discussion of the case law but submit that while it is possible to modify the prior art compounds, why would one have done so and with what reasonable expectation of success. In Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd., 87 USPQ2d 1452, 1454 (Fed. Cir. 2008), the Federal Circuit clarified the proof of obviousness in structural similarity situations such as this: ". . . Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 83 USPQ2d 1169 (Fed. Cir. 2007)." The key

phrase in the Federal Circuit's analysis is the "lead compound" and there are no teachings nor has the rejection established that the generic teachings in Wu and/or Takaya chosen from all of the compounds described in these documents. Indeed, this was clearly done in hindsight, which is improper, when considering the teachings of Wu and Takaya as a whole.

The articulated 3 element test for a *prima facie* case of obviousness based on structural similarity of a lead compound to a claimed compound is sound law and applicable here. (see, e.g., Procter & Gamble Co. v. Teva Pharms., USA, Inc. *566* F.3d 989, 90 U.S.P.Q.2D 1947 (Fed. Cir. 2009)) First, there must be a preliminary finding that one of ordinary skill···would have selected [the prior art compound] as a lead compound. There is no evidence that one would have done so and certainly no evidence as to why one of skill in the art would have modified Wu or Takaya's generic disclosure, which are in of themselves quite large, to make even further modifications from the thousands upon thousands of compounds embraced by Wu and Takaya.

Even post KSR, for a claimed invention to be obvious, the possible modifications of the prior art must be finite. *See*, Rolls-Royce PLC v. United Technologies Corp., 95 USPQ2d 1097 (Fed. Cir. 2010). As stated by the Federal Circuit:

> ***To determine that an invention would have been obvious*** to try on the basis of the record before the time of invention, ***this court has clarified***, with respect to inventions requiring selection of a species from a disclosed genus, ***that the possible approaches and selection to solve the problem must be*** "known and ***finite.***" *See Abbott*, 544 F.3d at 1351 (holding as conditions in which "obvious to try" may negate patentability, "the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option"). . . . In this case, the broad selection of choices for further investigation available to a person of ordinary skill included any degree of sweep. *See Takeda*, 492 F.3d at 1359 (holding the invention not obvious to try because the prior art disclosed a broad selection of compounds that an ordinarily skilled artisan could have selected for further investigation).

Rolls-Royce, at 1107, emphasis added.

This case is like that in Rolls-Royce in that there are countless possible theoretical modifications of the prior art with no teaching that any one modification should be selected. According to the Examiner's rationale Wu and/or Takaya's formulas can be varied in any number of positions (i.e., the variations are not limited to only those substituents that the Examiner specifically identified as variable). However, absent hindsight disclosure as to which compound to select and which substituent to change, any of the positions, indeed any of the rings or core could be changed. For example, looking at the compound number 2 in Wu that is reproduced on page 19 of the Action, , there are several positions that can be changed based on the Examiner's unsupported contention that it would have been obvious to change Wu's compounds, and likewise Takaya's. So but for hindsight to specifically select one position out of the many possible or so that are disclosed in Wu and Takaya the possible combination of substituents yields hundreds of thousands of possible combinations.

Thus, when one considers the citations as a whole it can be seen that the number of theoretical substitutions for compounds such as that of Claim 2 are exceedingly high. There are no teachings that would have led one of ordinary skill in the art to select one particular substitution cited in the Office Action. According to U.S. law the possible modifications of the prior art must be finite and as clear from the formulas provided in Wu and Takaya there are countless possible theoretical modifications of the prior art with no teaching that any one modification should be selected over another to arrive at the claimed compound.

Referencing again the three factor test, the second factor requires that a person of ordinary skill must have reason to attempt to make the claimed compound by modifying the lead compound. As the claimed compounds are targeted as PI3 kinase inhibitors, one would not have anticipated this activity simply based on the structure in the cited documents so there is no reason to modify the lead compound. Indeed, there is no evidence that adding a substitutient that would be required to alter each of the generic compounds is routine.

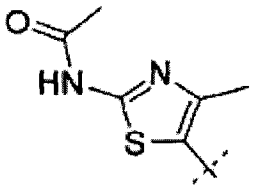
Third, there must be a reasonable expectation of success in making the claimed compound by modifying the lead compound. This does NOT mean only that there would be a reasonable expectation of being able to physically make the claimed compound – the requirement also encompasses a reasonable expectation that the resultant compound would be a "successful compound"and in terms of the present application, successful for PI3 kinase inhibitors or even the utilities taught by Wu and Takaya. The Examiner simply makes a conclusion that one would have reasonably expected similar activities but provides no evidence of this and, in fact, by doing so does not take into account the true nature of the unpredictability of the chemical arts. See also, Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., Id: "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

There are no teachings in the cited art to direct one of ordinary skill to modify the Wu and/or Takaya disclosure to arrive at the present claims which defines a limited selection of compounds that act on the Pi3K for the treatment of diseases that are different than the prior art. Even though the general disclosures that could have been applied to the claimed invention were known and within the level of skilled in the art the claims should be considered non-obvious because the problem which suggested the preparation of compounds active on Pi3K had been previously unknown as described by the present application (see page 7 of the present application). See the Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex (20Aug2010) 1358 OG 372 28SEP2010 75 Fed. Reg. 53643 01SEP2010 and Example 4.1. In re Omeprazole Patent Litigation, 536 F.3d 1361 (Fed.Cir. 2008).

Neither Wu nor Takaya address the problems identified by the inventors nor how one would devise a solution as has been found. In particular, a key finding of the present

invention is that how to achieve the claimed compounds while having activity on Pi3K and there are no teachings in Wu and Takaya that would lead one to improve on their compounds of such a complex chemical structure to specifically select compounds as defined in the claims. Indeed, the rejection screams of hindsight because as discussed the art used to allege obviousness are substantively different from that which is claimed.

To the Examiner's underlying motivation argument articulated on page 13 of the Action, it must be appreciated that even minor differences in the structure of the compound can have dramatic effects on it's activity. Indeed, this is shown by the data presented in the attached Rule 132 Declaration where compounds having the following group were found to be suitable for activity on Pi3K:



However, compounds having a different group, such as in the following example in the prior art are not suitable as they do not exhibit suitable activity compared to compounds of the present invention. See attached Rule 132 Declaration.

In view of the above and the amendments submitted in this paper, it is requested that the rejections be withdrawn.

A Notice of Allowance for all pending claims is also requested.

Respectfully submitted,

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